REMARKS

Claims 23, 25, 26, 29 and 31-39 are pending in this application. By this Amendment, claims 23 and 31 are amended, new claims 32-39 are added, and claims 24, 27, 28 and 30 are canceled. Support for the amendments to claims 23 and 31 may be found, for example, on page 4, lines 15-18; page 7, lines 3-5; and page 9, line 32. Additional support for the amendments to claim 31 may be found, for example, on page 9, lines 25-28. No new matter is added.

Applicants appreciate the courtesies shown to Applicants' representatives by Examiners Halvorson and Yu in the July 17, 2008 personal interview. Applicants' separate record of the substance of the interview is incorporated into the following remarks.

In view of the foregoing amendments and following remarks, reconsideration and allowance are respectfully requested.

I. Objection to Claim 31

The Office Action objects to dependent claim 31 for being broader than independent claim 23, from which claim 31 depends. By this Amendment, claim 31 is amended to be an independent claim. Accordingly, reconsideration and withdrawal of the objection are respectfully requested.

II. Rejections Under 35 U.S.C. §112

The Office Action rejects claims 23 and 31 under 35 U.S.C. §112, first paragraph for allegedly failing to meet the enablement requirement because "the specification, while being enabling for a method for the diagnosis of breast cancer, does not reasonably provide enablement for a method of therapeutic follow up, prognosis and the diagnosis of relapse in the case of breast cancer"; there is "no disclosure in the specification on the detection of NGF in blood, bone marrow, milk, cerebrospinal fluid, urine or effusions"; and "the specification has not provided guidance or examples to predict the therapeutic follow up, prognosis and the

diagnosis of relapse in the case of breast cancer by determining the presence of NGF in blood, bone marrow, milk, cerebrospinal fluid, urine and effusions." See pages 3-5. Applicants respectfully traverse this rejection.

A. The Specification is Enabling for a Method of Therapeutic Follow-Up and Diagnosis of Relapse in the Case of Breast Cancer

1. The Specification Provides Sufficient Description to Enable One of Ordinary Skill to Practice Therapeutic Follow-Up and Diagnosis of Relapse in the Case of Breast Cancer

The Office Action alleges that "the specification, while being enabling for a method for the diagnosis of breast cancer, does not reasonably provide enablement for a method of therapeutic follow up, prognosis and the diagnosis of relapse in the case of breast cancer." See pages 3 and 4.

Claim 23 does not recite a method of therapeutic follow-up, prognosis and diagnosis of relapse in the case of breast cancer. Applicants request withdrawal and reconsideration of the rejection of claim 23.

Without conceding the propriety of the rejection, claim 31 is amended to delete "prognosis." Applicants respectfully submit that the specification is enabling for a method of a therapeutic follow-up and diagnosis of relapse in the case of breast cancer, as recited by claim 31. Applicants also respectfully submit that the specification, at page 4, lines 22-29, and at page 9, lines 25-28, is enabling for a method of therapeutic follow-up and diagnosis of relapse in the case of breast cancer, as the same method may be used to determine the presence of breast cancer tissue in the first instance. Therefore, the specification enables one of ordinary skill in the art to practice the claimed method of a therapeutic follow-up and diagnosis of relapse in the case of breast cancer. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

2. No More Than Routine Experimentation by One of Ordinary Skill in the Art Would Have Been Required for Practicing the Claimed Invention

The Office Action also alleges that "the specification has not provided guidance or examples to predict the therapeutic follow up, prognosis and the diagnosis of relapse in the case of breast cancer by determining the presence of NGF in blood, bone marrow, milk, cerebrospinal fluid, urine and effusions" and relies on Tockman for teaching "considerations necessary in bringing a cancer biomarker to successful clinical application." See pages 4-5. As discussed in subsection A above, claim 23 does not recite a method of therapeutic follow-up, prognosis and diagnosis of relapse in the case of breast cancer. Applicants request withdrawal and reconsideration of the rejection against claim 23.

Without conceding the propriety of the rejection, claim 31 is amended to delete "prognosis" in the case of breast cancer, as well as "effusions." Because the Office Action relies on Slamon solely for the teaching of factors important in the prognosis of breast cancer, Slamon does establish any basis for finding non-enablement of amended claim 31. Applicants submit that because the specification provides sufficient guidance and thus is enabling for a "therapeutic follow-up and diagnosis of relapse in the case of breast cancer" as recited in claim 31, the teaching of Tockman does not establish any basis for finding non-enablement of the claims 31 or 23.

Tockman describes considerations necessary in bringing a biomarker to successful clinical application *once a biomarker has been identified.* See page 2713s (describing that in identifying and selecting a biomarker, "[i]f a biological change is to be an indicator of disease, it must produce a recognizable departure from "normal"; the "change" produces a difference from the mean or a usual value by an amount greater than is likely due to random or expected variability"). Also see page 2714s ("*Following* selection of a biomarker, the sensitivity and specificity of label-epitope binding in premalignant specimens must be

validated to a known (histology/cytology-confirmed) cancer outcome" (emphasis added)). Thus, Tockman teaches that once a biomarker has been identified, validation and screening of the biomarker required merely routine experimentation by one of ordinary skill in the art. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. See MPEP §2164.01, citing *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1998). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

Accordingly, as described in section VI of the attached 37 C.F.R. §1.132 Declaration, while identifying a substance that may act as a diagnostic tool in blood, bone marrow, milk, cerebrospinal fluid or urine is a challenging task requiring more than mere routine experimentation by one of ordinary skill in the art, the subsequent processes of validating and screening that diagnostic tool involve routine, and not undue, experimentation. Applicants have disclosed that determining the presence, in blood, bone marrow, milk, cerebrospinal fluid or urine, of NGF secreted by breast cancer cells can be used as a diagnostic tool for breast cancer. Therefore, bringing the secreted NGF to successful clinical application would have required merely routine experimentation from one of ordinary skill in the art. Accordingly, Applicants submit that the specification is enabling for the therapeutic follow-up and diagnosis of relapse in the case of breast cancer by "determining the presence, in a biological sample, ... of [NGF] that has been secreted by breast cancer tissue; wherein the biological sample comprises a substance selected from the group consisting of: blood, bone

marrow, milk, cerebrospinal fluid and urine." Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

B. The Specification is Enabling for Detection of NGF in Blood, Bone Marrow, Milk, Cerebrospinal Fluid and Urine

The Office Action also alleges that there is "no disclosure in the specification on the detection of NGF in blood, bone marrow, milk, cerebrospinal fluid, urine or effusions." See page 4.

By this Amendment, claims 23 and 31 are amended to delete "effusions." The specification is enabling for "determining the presence, in a biological sample, ... of [NGF] that has been secreted by breast cancer tissue; wherein the biological sample comprises a substance selected from the group consisting of: blood, bone marrow, milk, cerebrospinal fluid and urine," as recited in independent claims 23 and 31. The specification describes that "[t]he biological sample used for the direct detection of NGF, liable to contain NGF as such, may consist of biological fluid or a tissue originating from the biopsy of the [breast cancer] tumor or the metastases of the patient under consideration. By biological fluid, mention may be made of *blood, bone marrow, milk, cerebrospinal fluid, urine* and effusions" (emphasis added). See page 6, line 37 to page 7, lines 2. NGF is a protein. The specification describes that "[t]he direct detection of NGF in the biological sample can be carried out by any means known to those skilled in the art." See page 4, lines 38-39. A wide variety of suitable methods for detection is disclosed on pages 5 and 6 of the specification, such as ELISA, IRMA, RIA, "competition" methods and mass spectrometry, among others. These various methods are common protein detection techniques that were well known to one of ordinary skill in the art. Accordingly, the specification is fully enabling for a method of "determining the presence, in a biological sample, ... of [NGF] that has been secreted by breast cancer tissue; wherein the biological sample comprises a substance selected from the group

consisting of: blood, bone marrow, milk, cerebrospinal fluid and urine," as recited in independent claims 23 and 31. Therefore, reconsideration and withdrawal of the rejection are respectfully requested.

III. Rejections Under 35 U.S.C. §103(a)

The Office Action rejects claims 23, 24-27, 29 and 30 under 35 U.S.C. §103(a) as allegedly having been obvious over Sakamoto in view of Ts'o and further in view of Varilek; rejects claim 28 under 35 U.S.C. §103(a) as allegedly having been obvious over Sakamoto in view of Ts'o and Picker; and rejects claims 23 and 31 under 35 U.S.C. §103(a) as allegedly having been obvious over Sakamoto in view of Bigazzi and further in view of Pica. Applicants respectfully traverse the rejections.

A. Claim Amendments

1. Independent Claims 23 and 31 are Amended

By this Amendment, claim 31 is amended to be an independent claim. Also by this Amendment, independent claims 23 and 31 are amended to recite, in part, "determining the presence, in a biological sample, ... of [NGF] that has been secreted by breast cancer tissue; wherein the biological sample comprises a substance selected from the group consisting of: blood, bone marrow, milk, cerebrospinal fluid and urine." Accordingly, the claims require a method of determining the presence of NGF in blood, bone marrow, milk, cerebrospinal fluid or urine, wherein the NGF has been secreted by breast cancer tissue, rather than being present in breast cancer cells. Notably, the claims are not directed to determining the presence of NGF in tissue or cells of any type, particularly circulating tumor cells that might be found in blood, bone marrow, milk, cerebrospinal fluid or urine.

2. Claim 28 is Canceled

By this Amendment, claim 28 is canceled, thereby rendering its rejection moot. Accordingly, reconsideration and withdrawal of the rejection of claim 28 are respectfully requested.

B. The Office Action Improperly Combined the Applied References

The Office Action's combinations of the teachings of: 1) Sakamoto, Ts'o and Varilek; and 2) Sakamoto, Bigazzi and Pica are based on impermissible application of hindsight, and are improper for several reasons. First, it would not have been obvious to one of ordinary skill in the art to try the applied combination of the references because there would have been no reasonable expectation of success in doing so, and because the claimed invention achieves unexpected results.

> "[A] person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely that the [method was] not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103."

MPEP §2143, citing *KSR Int. Co. v. Teleflex, Inc.*, 82 U.S.P.Q.2d, 1385 at 1397 (2007).

However, as discussed below, it would not have been obvious from the teachings of the applied references that elevated levels of NGF present in breast cancer tissue correlated to elevated levels of NGF secreted by breast cancer tissue present in blood, bone marrow, milk, cerebrospinal fluid, or urine. Therefore, there would not have been a reasonable expectation of success in looking for the presence, in blood, bone marrow, milk, cerebrospinal fluid, or urine, of NGF secreted by breast cancer tissue as a diagnostic tool for breast cancer.

Moreover, as discussed below, it was improper for the Office Action to combine the applied references because there would have been no reason to do so and the claimed invention produces unexpected results. Further still, even the improper combination would

not have produced the claimed invention. For at least these reasons, the applied references, alone or in combination, would not have rendered the claimed invention obvious.

1. <u>There Would Have Been No Reasonable Expectation of Success</u>

The applied references, alone or in combination, would not have rendered obvious the claimed invention because there would have been no reasonable expectation of success from combining and modifying the teachings of the applied references to produce the claimed invention. None of the applied references, alone or in combination, teach or suggest that the NGF secreted by breast cancer tissue is present in blood, bone marrow, milk, cerebrospinal fluid and urine in levels sufficient to be a useful diagnostic tool for breast cancer. In fact, of all of the applied references, only Sakamoto teaches that NGF is secreted by breast cancer cells. However, Sakamoto teaches that the NGF is involved in both a paracrine and an autocrine loop. See page 977. Additionally, Sakamoto does not teach how much, if any, of the secreted NGF enters or remains in the blood, bone marrow, milk, cerebrospinal fluid or urine. Therefore, Sakamoto fails to teach or suggest "determining the presence, in a biological sample, ... of [NGF] that has been secreted by breast cancer tissue; wherein the biological sample comprises a substance selected from the group consisting of: blood, bone marrow, milk, cerebrospinal fluid and urine," as recited by independent claims 23 and 31.

Furthermore, section V of the attached 37 C.F.R. §1.132 Declaration describes that NGF was known to have a very short half-life (varying from less than one to five hours according to the experimental procedures, see attached references[1]). The short half-life of NGF would have made it even more unpredictable for the presence of secreted NGF to be

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[1] Tria, M.A., Fusco, M., Vantini, G., Mariot R., *Pharmacokinetics of Nerve Growth Factor (NGF) Following Different Routes of Administration to Adult Rats*. Exp. Neurol.,127(2):178-83 (1994).

Tandrup, T., Vestergaard, S., Tomlinson, D. R., Diemel, L. T., Jakobsen, J., *The structural effect of systemic NGF treatment on permanently axotomised dorsal root ganglion cells in adult rats*, J. Anat., 194(3): 373-379, (Apr. 1999).

Krewson, C. E., Saltzman, W. M. *Transport and elimination of recombinant human NGF during long-term delivery to the brain*, Brain Research, 727(2): 169-181 (1996).

detected in blood, bone marrow, milk, cerebrospinal fluid and urine. Secreted NGF in the blood quickly binds to spinal nodes rich in TRKa receptors, thereby depleting the secreted NGF from the blood. This also would have made it even more unpredictable for the presence of NGF to be detected in blood. See section V of the attached 37 C.F.R. §1.132 Declaration. Therefore, it would also not have been obvious to one of ordinary skill in the art to try the combination of the applied references because one of ordinary skill in the art would not have reasonably anticipated that such an effort would be successful.

2. <u>The Claimed Invention Achieves Unexpected Results</u>

The claimed invention achieves unexpected results. Thus, it would also not have been obvious to one of ordinary skill in the art to try the combination of the applied references for that additional reason. The Applicants have unexpectedly discovered that the overexpression of NGF in breast cancer tissue correlates to an increased level of NGF secreted by breast cancer tissue present in blood, bone marrow, milk, cerebrospinal fluid and urine. However, a change in the level of a protein secreted by cancerous tissue does not necessarily correlate with a similar change in the level of that protein in blood, bone marrow, milk, cerebrospinal fluid or urine. As described sections I-III of the attached 37 C.F.R. §1.132 Declaration, at the time of the claimed invention, it would not have been predictable that the change in the level of NGF in tissue would have correlated to a similar change in the level of secreted NGF present in blood, bone marrow, milk, cerebrospinal fluid and urine in levels sufficient to be a useful diagnostic tool for breast cancer.

A change in the level of a protein secreted by cancerous tissue does not necessarily correlate to a similar change in the level of the secreted protein present in blood, bone marrow, milk, cerebrospinal fluid or urine. Accordingly, a change in the level of NGF in breast cancer tissue, as taught by Sakamoto, would not have automatically correlated to a similar change of the level of secreted NGF in such substances.

For example, Experimentation 1 in the attached Declaration shows that an increased level of a protein secreted by colorectal cancer tissue does not correlate to an increased level of the secreted protein in blood, even though the protein is secreted by the cancerous tissue. Immunohistochemical analysis shows overexpression of the protein in tissues of cancer patients, as well as tissues of patients having benign lesions, as compared to tissues of healthy subjects. However, levels of this secreted protein in the blood of both cancer patients and healthy subjects are equivalent. This demonstrates that overexpression of a protein in cancer tissue does not necessarily lead to an increase in the secreted protein in the blood, even though the protein is secreted by the tissue. Consequently, determining the presence in a biological sample of the protein secreted by the cancerous tissue could not have been expected to be useful for diagnosis of the cancer, wherein the biological sample comprises a substance selected from the group consisting of: blood, bone marrow, milk, cerebrospinal fluid and urine.

In contrast, the claimed invention is demonstrated by the results of Experimentation 2 in the attached Declaration, which shows that an increased level of NGF present in breast cancer tissue correlates with an increased level of secreted NGF in blood. Immunohistochemical analysis of breast cancer tissue and normal mammary tissue shows expression of NGF in tissues of breast cancer patients, while the normal mammary tissues show no NGF expression. The level of secreted NGF present in the blood of patients with breast cancer is higher than the level of secreted NGF present in the blood of healthy patients. This demonstrates that in the case of NGF and breast cancer, expression of NGF in breast cancer tissue does correlate to the presence of elevated levels of secreted NGF present in the blood. Accordingly, an increased level of NGF secreted by breast cancer tissue in the blood unexpectedly can be used in diagnosing breast cancer.

The results of Experimentation 1 show that it would not have been predictable that the secretion of a protein by cancerous tissue would have correlated to the presence of the secreted protein in samples such as blood, bone marrow, milk, cerebrospinal fluid and urine. Accordingly, it would not have been predictable that the secretion of NGF by breast cancer tissue would have correlated to elevated levels of secreted NGF present in blood, bone marrow, milk, cerebrospinal fluid and urine, and it would not have been obvious to one of ordinary skill in the art to try the combination of the applied references. Applicants have unexpectedly discovered that the secretion of NGF by breast cancer tissue correlates to elevated levels of secreted NGF present in bodily fluids, such as blood, bone marrow, milk, cerebrospinal fluid and urine and that such correlation can be used in the claimed methods.

3. There Would Have Been No Reason To Combine Sakamoto, Bigazzi and Pica

The Office Action rejects claims 23 and 31 as allegedly having been obvious over Sakamoto in view of Bigazzi and further in view of Pica. Page 7 of the Office Action alleges that "[o]ne of ordinary skill in the art would have been motivated to apply Bigazzi et al and Pica et al's detection of NGF in the serum to Sakamoto et al's method for diagnosing breast cancer by using immunohistochemistry on biopsy specimens to detect NGF because of the simplicity of detecting a tumor antigen in serum as opposed to a tissue biopsy." However, there would have been no reason for one of ordinary skill in the art to combine the applied references. Therefore, this rejection is respectfully traversed.

As discussed above, Sakamoto fails to teach or suggest "determining the presence, in a biological sample, ... of [NGF] that has been secreted by breast cancer tissue; wherein the biological sample comprises a substance selected from the group consisting of: blood, bone marrow, milk, cerebrospinal fluid and urine," as recited by claims 23 and 31.

Bigazzi fails to cure the deficiencies of Sakamoto. Bigazzi teaches that the level of an unidentified factor was increased in the serum of a single patient afflicted with a rare disease, a familial medullary thyroid carcinoma associated with a complex hereditary syndrome. The patient suffered from sympathetic nervous system pathologies associated with the thyroid carcinoma. See page 105. The Office Action, on page 7, relies on Bigazzi for the teaching of detecting NGF in the serum. However, Bigazzi's teachings are directed to thyroid cancer, and Bigazzi is silent as to breast cancer. One of ordinary skill in the art would have appreciated that thyroid cancer is histopathologically and physiologically different from breast cancer. See section IV of the attached 37 C.F.R. §1.132 Declaration. Furthermore, Bigazzi merely speculates that the factor found in the serum of the patient was NGF, but does not conclusively identify the factor as NGF. See page 105 of Bigazzi, describing that the patient's serum had "high levels of a factor, *probably circulating human nerve growth factor*" (emphasis added). See also page 108, describing that "the material identified [as being present in the serum] was not proved to be human NGF." Moreover, Bigazzi was published in 1976, when no assay methods were available that would have positively identified the factor as NGF. See section IV of the attached 37 C.F.R. §1.132 Declaration. Yet further still, the patient's son, who was apparently clinically normal (i.e., had no tumors that could produce and excrete a biomarker) had high levels of the unidentified factor in the serum. See page 105. In light of the son's complex hereditary pathology, this strongly indicates that the unidentified factor was released into the serum from a source other than tumor cells. See section IV of the attached 37 C.F.R. §1.132 Declaration. Accordingly, Bigazzi's teaching is, at best, a single case study of a patient suffering from a medical anomaly, and is heavily laden with speculation. Bigazzi thus fails to: 1) conclusively identify the presence of NGF in the serum; 2) conclusively identify that the source of the secreted unidentified protein in the serum was cancerous tissue; or 3) teach or suggest determining the presence, in a biological

sample, of NGF that has been secreted from breast cancer tissue, wherein the biological sample comprises a substance selected from the group consisting of blood, bone marrow, milk, cerebrospinal fluid and urine.

Pica also fails to cure the deficiencies of Sakamoto. Pica discusses the relationship between NGF serum levels, human herpesvirus-8 and Kaposi's sarcoma (KS). See page 2028. The Office Action, on page 7, also relies on Pica for the teaching of detecting NGF in the serum. However, Pica is silent as to breast cancer altogether. Moreover, Pica does not teach or suggest that the KS tissue secretes NGF, and therefore fails to teach or suggest that the source of the NGF present in the serum is the KS tissue.

There would have been no reason for one of ordinary skill in the art to combine the teachings of Sakamoto, Bigazzi and Pica. As described above, Sakamoto teaches that NGF is found in breast cancer cells, but the claimed invention is not directed to determining the presence of NGF in breast cancer cells. Bigazzi teaches that high levels of an unidentified factor was found in the serum of one patient with a rare disease, but Bigazzi fails to conclusively identify the presence of NGF in the serum, and also fails to conclusively identify that the source of the unidentified protein in the serum was cancerous tissue. Moreover, the fact that the patient's son, who had no tumors, had elevated levels of unidentified protein in his blood strongly indicates that the source of serum NGF was not cancerous tissue. Therefore, because Bigazzi's highly speculative teachings fail to teach or suggest a correlation between serum NGF levels and NGF secretion by cancerous tissue, there would have been no reason for one of ordinary skill in the art to combine the teachings of Sakamoto and Bigazzi. Furthermore, Pica discusses the relationship between NGF serum levels and Kaposi's sarcoma (KS), but Pica fails to teach or suggest that the KS tissue secreted NGF, and fails to teach or suggest that the source of the serum NGF was the KS tissue. Because Pica also fails to teach or suggest a correlation between serum NGF levels and NGF secretion by KS tissue, there

would have been no reason for one of ordinary skill in the art to combine the teachings of Sakamoto, Bigazzi and Pica.

4. The Improper Combination Would Not Have Produced the Claimed Invention

Even the improper combination would not produce the claimed invention. As described above, each of the applied references fails to teach or suggest "determining the presence, in a biological sample, ... of [NGF] that has been secreted by breast cancer tissue; wherein the biological sample comprises a substance selected from the group consisting of: blood, bone marrow, milk, cerebrospinal fluid and urine," as recited by independent claims 23 and 31.

At most, Sakamoto teaches that NGF is secreted by breast cancer tissues. However, Sakamoto fails to teach or suggest that the NGF secreted by the breast cancer tissue can be found in the blood, bone marrow, milk, cerebrospinal fluid and urine.

Ts'o fails to cure the deficiencies of Sakamoto. The Office Action relies on Ts'o only for its teaching of a method of enriching cancer cells from bodily fluids and alleges that "[o]ne of ordinary skill in the art would have been motivated to apply [Ts'o's] method of enriching cancer cells from bodily fluids to Sakamoto et al's method for diagnosing breast cancer by detecting NGF because enriching for and detecting *cancer cells* in the peripheral blood would be of great diagnostic benefit" (emphasis added). See page 6. However, the claimed invention is directed to detecting the presence of secreted NGF present in blood, bone marrow, milk, cerebrospinal fluid or urine; the claimed invention is not directed to detecting *cancer cells*, or even NGF present within cancer cells, in the blood, bone marrow, milk, cerebrospinal fluid and urine. In fact, Ts'o is silent as to NGF altogether.

Varilek also fails to cure the deficiencies of Sakamoto. Varilek teaches that a human colon adenocarcinoma and a nonmalignant enterocyte cell line derived from fetal rat intestine

produce and secrete NGF. See page G445. However, Varilek fails to teach or suggest that secreted NGF is found in the blood, bone marrow, milk, cerebrospinal fluid or urine of the humans with colon adenocarcinoma and/or the fetal rats with nonmalignant enterocyte. Varilek also fails to teach or suggest that the presence of NGF in the tissues of human patients with colon adenocarcinoma or fetal rats with nonmalignant enterocyte correlates to the presence of secreted NGF in the blood, bone marrow, milk, cerebrospinal fluid or urine of the human patients and fetal rats. Moreover, Varilek is silent as to breast cancer altogether. Colon adenocarcinoma and nonmalignant enterocyte are histopathologically and physiologically different from breast cancer.

As discussed in section III.B.3. above, Bigazzi and Pica also fail to cure the deficiencies of Sakamoto.

Therefore, the element of "determining the presence, in a biological sample, ... of [NGF] that has been secreted by breast cancer tissue; wherein the biological sample comprises a substance selected from the group consisting of: *blood, bone marrow, milk, cerebrospinal fluid and urine*" (emphasis added) recited in claim 23 would be missing from the combination of Sakamoto, Ts'o and Varilek. Accordingly, the combination of Sakamoto, Ts'o and Varilek would not produce the claimed invention of independent claims 23 and 31. Likewise, because the same element would missing from the improper combination of Sakamoto, Bigazzi and Pica, the improper combination of Sakamoto, Bigazzi and Pica would not produce the claimed invention of independent claims 23 and 31.

For at least the foregoing reasons, Sakamoto, Varilek and Ts'o, alone or in combination, would not have rendered obvious independent claim 23 and the claims dependent therefrom. Likewise, Sakamoto, Bigazzi and Pica, alone or in combination, would not have rendered obvious claims 23 and 31. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

IV. Conclusion

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of this application are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,

Hee H Smith

William P. Berridge
Registration No. 30,024

Hee H. Smith
Registration No. 57,631

WPB:HHS/jth

Attachments:

Declaration Under 37 C.F.R. §1.132

Tria, M.A., Fusco, M., Vantini, G., Mariot, R., *Pharmacokinetics of Nerve Growth Factor (NGF) Following Different Routes of Administration to Adult Rats*. Exp. Neurol.,127(2):178-83 (1994).

Tandrup, T., Vestergaard, S., Tomlinson, D. R., Diemel, L. T., Jakobsen, J., *The structural effect of systemic NGF treatment on permanently axotomised dorsal root ganglion cells in adult rats*, J. Anat., 194(3): 373-379, (Apr. 1999).

Krewson, C. E., Saltzman, W. M. *Transport and elimination of recombinant human NGF during long-term delivery to the brain*, Brain Research, 727(2): 169-181 (1996).

Date: July 22, 2008

OLIFF & BERRIDGE, PLC
P.O. Box 320850
Alexandria, Virginia 22320-4850
Telephone: (703) 836-6400

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